

PATENT COOPERATION TREATY

0964631

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Assistant Commissioner for Patents
 United States Patent and Trademark
 Office
 Box PCT
 Washington, D.C. 20231
 ÉTATS-UNIS D'AMÉRIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 17 November 1999 (17.11.99)	Applicant's or agent's file reference RM/X89258/PC
International application No. PCT/IT99/00063	Priority date (day/month/year) 18 March 1998 (18.03.98)
International filing date (day/month/year) 18 March 1999 (18.03.99)	
Applicant PAGLIARO, Mario et al	

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:
 15 October 1999 (15.10.99)

☐ in a notice effecting later election filed with the International Bureau on:

2. The election ☒ was
☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO
 34, chemin des Colombettes
 1211 Geneva 20, Switzerland

Authorized officer

Olivia RANAIVOJAONA

Facsimile No.: (41-22) 740.14.35

Telephone No.: (41-22) 338.83.38

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference RM/X89258/PC	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/IT 99/ 00063	International filing date (day/month/year) 18/03/1999	(Earliest) Priority Date (day/month/year) 18/03/1998
Applicant CONSIGLIO NAZIONALE DELLE RICERCHE.et.al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☐ **Certain claims were found unsearchable** (See Box I).

3. ☐ **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

☐ the text is approved as submitted by the applicant.

☒ the text has been established by this Authority to read as follows:

CATALYTIC MATERIALS FOR SELECTIVE OXIDATION OF ALCOHOLS, PROCESS FOR PRODUCTION THEREOF AND THEIR USE IN ALCOHOL OXIDATION PROCESS

5. With regard to the **abstract**,

☐ the text is approved as submitted by the applicant.

☒ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.

☐ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

☒ None of the figures.

Box III TEXT OF THE ABSTRACT (Continuation of item 5 of the first sheet)

A versatile methodology to obtain efficient catalytic materials suitable for selective, liquid-phase oxidations of alcohols is described. Solid inorganic membranes were prepared by the sol-gel procedure by adding a solution of stable organic nitroxyl radicals at the onset of the polymerization of silicon alkoxide monomers. In this way, micro- and mesoporous materials can be obtained that are effective and recyclable catalytic mediators for highly selective oxidations of a vast class of primary and secondary alcohols carried out with several primary oxidants. Delicate substrates such as carbohydrates and allylic alcohols can selectively be oxidised with these novel catalytic materials.

INTERNATIONAL SEARCH REPORT

International Application No

/IT 99/00063

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 B01J31/02 B01J37/03 C07C51/235

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 B01J C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	A. SHAMES ET AL.: "In situ EPR study of sol-gel processes" JOURNAL OF NON-CRYSTALLINE SOLIDS, vol. 175, 1994, pages 14-20, XP002108351 cited in the application see page 15, column 2 ---	1-23,41, 44
X	KAZUNORI MATSUI ET AL.: "ESR Study of a Nitroxide Radical in Sol-Gel Glasses" JOURNAL OF SOL-GEL SCIENCE AND TECHNOLOGY, vol. 9, 1997, pages 273-277, XP002108352 cited in the application see page 274, column 1 ---	1-23,41, 44
	--- -/--	

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

6 July 1999

Date of mailing of the international search report

21/07/1999

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Schwaller, J-M

INTERNATIONAL SEARCH REPORT

International Application No

/IT 99/00063

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	HEERES A. ET AL.: "Synthesis of alpha and beta-D-glucopyranonate 1-phosphate and alpha-D-glucopyranuronate 1-fluoride: intermediates in the synthesis of D-glucuronic acid from starch" CARBOHYDRATE RESEARCH, vol. 299, 1997, pages 221-227, XP002108353 cited in the application ---	
A	US 5 292 801 A (D. AVNIR ET AL.) 8 March 1994 cited in the application -----	

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

/IT 99/00063

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5292801 A	08-03-1994	IL 93134 A	20-11-1997
		AT 166459 T	15-06-1998
		DE 69129422 D	25-06-1998
		DE 69129422 T	07-01-1999
		EP 0439318 A	31-07-1991
		JP 6122521 A	06-05-1994
		US 5650311 A	22-07-1997
		US 5300564 A	05-04-1994
		US 5824526 A	20-10-1998
		US 5371018 A	06-12-1994
		US 5308495 A	03-05-1994

**COURTESY COPY OF THE
INTERNATIONAL PRELIMINARY
EXAMINATION REPORT WITH ANNEXES
CONTAINING SPECIFICATION PAGES
4, 5, 7, 8, 13 AND NEW CLAIMS
1-18 TO BE SUBSTITUTED FOR THE
ORIGINAL SPECIFICATION PAGES 4,
5, 7, 8, 13 AND THE ORIGINAL
CLAIMS FOR EXAMINATION IN
THIS CASE**


PATENT COOPERATION TREATY

PCT

REPLACED BY
ART 34 AMDT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference RM/X89258/PC		FOR FURTHER ACTION		See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/IT99/00063	International filing date (day/month/year) 18/03/1999	Priority date (day/month/year) 18/03/1998		
International Patent Classification (IPC) or national classification and IPC B01J31/02				
Applicant CONSIGLIO NAZIONALE DELLE RICERCHE.et.al.				
<p>1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 4 sheets, including this cover sheet.</p> <p><input checked="" type="checkbox"/> This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).</p> <p>These annexes consist of a total of 9 sheets.</p>				
<p>3. This report contains indications relating to the following items:</p> <ul style="list-style-type: none"> I <input checked="" type="checkbox"/> Basis of the report II <input type="checkbox"/> Priority III <input type="checkbox"/> Non-establishment of opinion with regard to novelty, inventive step and industrial applicability IV <input type="checkbox"/> Lack of unity of invention V <input checked="" type="checkbox"/> Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement VI <input type="checkbox"/> Certain documents cited VII <input type="checkbox"/> Certain defects in the international application VIII <input type="checkbox"/> Certain observations on the international application 				
Date of submission of the demand 15/10/1999		Date of completion of this report 14.06.2000		
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465		Authorized officer Schwaller, J-M Telephone No. +49 89 2399 8351		



INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/IT99/00063

I. Basis of the report

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.)*:

Description, pages:

1-3,6,9-12, 14-18	as originally filed			
4,5,7,8,13	as received on	19/04/1999	with letter of	07/04/1999

Claims, No.:

1-18	with telefax of	10/05/2000
------	-----------------	------------

2. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims 1-18
	No:	Claims
Inventive step (IS)	Yes:	Claims 1-18
	No:	Claims
Industrial applicability (IA)	Yes:	Claims 1-18
	No:	Claims

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/IT99/00063

2. Citations and explanations

see separate sheet

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/IT99/00063

Re Item V**Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

The closest prior art to the present application is represented by the document:
HEERES A. et al.: "Synthesis of alpha and beta-D-glucopyranonate 1-phosphate and alpha-D-glucopyranuronate 1-fluoride: intermediates in the synthesis of D-glucuronic acid from starch", CARBOHYDRATE RESEARCH, vol. 299, 1997, p. 221-227 (D3)
which discloses a catalyst prepared by immobilization of a nitroxyl radical containing-compound (OTEMPO) on commercial amino-functionalised silica and its use for the conversion of a carbohydrate into its carboxyl derivative.

The subject-matter claimed **distinguishes therefrom** in that the supporting material is obtained by a sol-gel process and this material is itself coated on a mesoporous inorganic support (Novelty)

This new material shows high selectivity and yields (both close to 100 %) as well as a long-term durability while the prior art materials have a rapid decrease of their activity (see comparative tests); accordingly an **inventive step** can be recognized thereto.

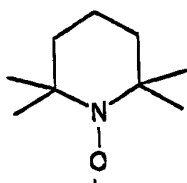
WO 99/47258

PCT/IT99/00063

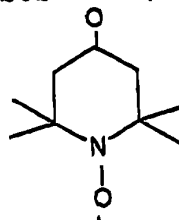
- 4 -

catalytic activity. The Authors therefore suggest the use of di-*t*-but-azodicarboxylate (DBAD) as a better primary oxidant affording less carbonate burden (10% equiv.) [I.E. Markó, P.R. Giles, M. Tsukazaki, S.M. Brown, C.J. Urch, *Angew. Chem. Int. Ed. Engl.*, 36 (1997) 2208-2210]. Another novel catalytic reaction system has been introduced in Japan where alcohols are oxidised with 30% H₂O₂ in the presence of catalytic tungsten complexes with high turnover numbers [R. Nogori, K. Sato, M. Aoki, J. Takahi, *J. Am. Chem. Soc.*, 119 (1997) 12386-12390].

Highly promising candidates suitable for the preparation of efficient heterogeneous catalysts may originate from stable organic nitroxyl radicals. These are di-tertiary-alkyl nitroxyl radicals (Figure 1) with A representing a chain of two or three atoms (methylene groups) or a combination of one or two atoms with an oxygen or nitrogen atom as described in International patent application PCT/NL94/00217. Typically, the preferred radicals employed belong to the family of the 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO, 1) and its derivatives substituted in position 4 (4-oxo-TEMPO, 2).



1



2

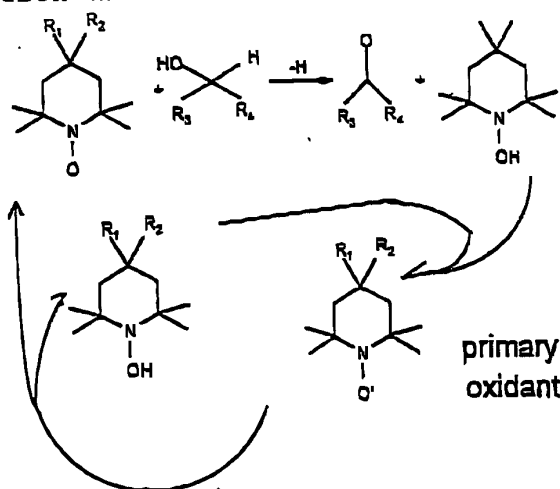
These species are highly efficient and versatile catalysts suitable for highly selective oxidation of hydroxyl containing compounds either to carbonyl or to carboxyl compounds, depending on applied reaction conditions. Their use as catalytic mediators in alcohol oxidations has been recently reviewed in depth in [A.E.J.

WO 99/47258

PCT/IT99/00063

- 5 -

de Nooy, A.C. Besemer, H. van Bekkum, *Synthesis*, (1996) 1153-1174]. Reactions can be carried out both at acidic and alkaline pH's with important difference in the selectivity observed. Furthermore, the oxidation reaction can be performed in different reaction media, i.e. in organic solvent, in biphasic water-organic solvent system and in water. In these catalytic oxidations, the active species (oxidant) is the (cyclic) nitrosonium ion which is generated in situ by adding an active primary oxidant including, among the others, Cu (II), NaOCl, NaOBr, NaBrO₂, N₂O₄, K₃Fe(CN)₆. It is believed that positive nitrogen of the cyclic nitrosonium ion attacks the alcoholic oxygen, with subsequent hydride abstraction in a bielectronic oxidative step involving carbonyl formation and acid release in the reaction mixture.



The hydroxylamine formed in the oxidative step disproportionates with the free radical to yield the nitrosonium ion or is directly oxidised with the primary oxidant to nitrosonium ion in a bielectronic reaction. As stated above, several alcoholic substrates can be oxidised at completion with high reaction rate and remarkable selectivity (compatibility with other oxidisable groups) and while alcohol oxidation in organic

25

WO 99/47258

PCT/IT99/00063

- 7 -

In the carbohydrate industry, oxidation is a useful means to obtain products of high added value starting from low cost, non toxic and readily available materials [K. van der Wiele, Carbohydrates in Europe, 13 (1995) 3].

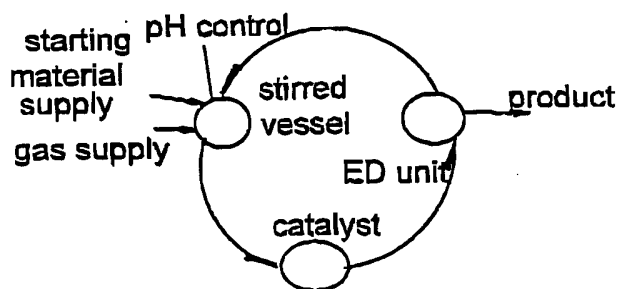
5 Mono-oxidised sugars are the products of commercial interest but, due to the chemical similarity of different alcoholic groups in sugars, the selectivity of most chemical oxidants is low. Thus, often protection-deprotection steps of different oxidisable hydroxyls are

10 required before and after the chemical oxidative step, as in the case of the commercial production of ascorbic acid (vitamin C) from a sorbose derivative. Accordingly, the introduction of new selective catalytic processes to substitute the traditional stoichiometric oxidations is

15 the object of intense research efforts. New stable bimetallic (Pd-Bi/C) catalysts have been recently introduced for the preparation of mono-oxidised sugars; the catalyst Palatinose® (Pt/C) is used in an efficient, continuous catalytic process for the oxidation of D-

20 glucose to D-gluconate. in which air is bubbled in an aqueous glucose solution and the reaction product is separated by electrophoresis while the sugar is continuously processed [M. Kunz et al., German patent DE OS 43 07 388 A1]

25



In contrast to D-gluconic acid, D-glucuronic acid is not produced on an industrial scale despite its

WO 99/47258

PCT/IT99/00063

- 8 -

considerable importance [M. Boiret, A. Marty, J. Chem. Ed., 63 (1986) 1009-1011]. Its synthesis on a small scale is carried out with an enzyme and the price of the resulting compound is high. Moreover, native carbohydrate polymer containing carboxylic group at C-6 (polyuronates) find many commercial applications due to their remarkable properties as complexing agents and for abilities to form gels at low-concentrations (hyaluronanes, pectins, xanthan etc). A major breakthrough in the commercially relevant field of carbohydrate oxidations occurred therefore with the introduction of the regioselective homogeneous oxidation of carbohydrate primary alcohols into carboxylic acids mediated by nitroxyl radicals as described in PCT/NL94/00217. By using NaOBr as stoichiometric oxidant together with a catalytic amount of the radical 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) at alkaline pH (10) and low temperature (2° C), sugars protected at the anomeric center are rapidly and selectively converted into respective uronates,



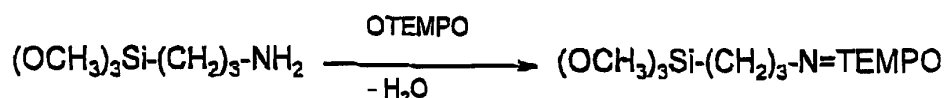
Due to a cyclic reaction mechanism, this alkaline oxidation method affords the rapid (80 min) regioselective primary alcohols oxidation of soluble polymeric carbohydrates (i.e. starch, inulin, pullulan) affording highly valuable and pure solution of the corresponding polyuronate. The use of NaOBr in place of NaOCl significantly increases the reaction rate. At pH 10 reaction rate is fastest while the non-selective oxidation of sugars by hypohalite has a much lower reaction rate and no side products are detected apart from the uronate. A recent comparative study clearly

WO 99/47258

PCT/IT99/00063

- 13 -

both physically and chemically entrapped. Physical entrapment was carried out with TEMPO by adding the oxidant to the initial polymerizing mixture. Covalent entrapment was conducted by mixing 3-aminopropyl trimethoxysilane [NH₂-CH₂CH₂CH₂-Si(OCH₃)₃] with a solution of 4-oxo-TEMPO in methanol followed by reduction of the immine thereby formed. The precursor monomer is further polymerized with tetramethoxyorthosilicate (TMOS) according to the sol-gel procedure.



The polycondensation of alkoxysilanes is associated with gelation of the sol, which after drying is densified by mild heat treatment to form a porous glass. The properties of the final glass are determined by the chemical and physical conditions during the preparation process. They depend upon the ratio metal/water (r), the amount of added alcohol, the alkoxide, the pH, the type of the acid/base catalyst, the temperature, the drying time and the amounts of added organic additives such as surfactants. Pore size and surface area are controlled by variations of all of these parameters. Hence, selection of optimal parameters is an important aspect of this invention. The following description of experiments are typical examples for such optimal procedures, but they are given without losing generality from the point of view of variations in these procedures which are obvious to the person skilled in the field.

EXAMPLES

Preparation of sol-gel glasses doped with nitroxyl radicals was conducted as follows.

WO 99/47258

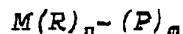
PCT/IT99/00063

- 19 -

CLAIMS

1. A process for the preparation of catalytic materials for the oxidation of alcohols by means of entrapment of stable nitroxyl radicals in sol-gel glassy matrixes, characterised in that it comprises the steps of:

a) preparing a polymerizing mixture comprising at least a monomer of the formula



wherein M is a semi- or a metal element,

R is a hydrolyzable substituent

n is an integer of 1 to 6,

P is a non-polymerizable substituent, and

m is an integer of 0 to 6;

water and an alcohol promoting the mixability of said monomer with the water;

b) additioning to said mixture a stable organic nitroxyl radical selected from the group comprising the 2,2,6,6,-piperidin-1-oxyl, also denominated TEMPO, the precursors and derivatives;

c) additioning water to the said mixture; and

d) hydrolize and polycondense the monomers defined at step a) to obtain a gel.

2. The process according to claim 1, wherein in the step c) a catalyst is additioned.

3. The process according to claim 1 or 2, further comprising the steps of

e) curing said gel at a temperature lower than 200°C in order to promote the complete polycondensation, solvent evaporation and the obtaining of a dry gel, also denominated xerogel; and

f) drying said xerogel by a mild thermal treatment performed at a temperature lower than 200°C.

4. The process according to any one of claims 1 to 3, wherein M is Si, Ti, Pb or Al.

5. The process according to any one of claims 1 to 5, wherein R is an alkoxy or arylalkoxy group.

WO 99/47258

PCT/IT99/00063

- 20 -

6. The process according to any one of claims 1 to 5, wherein n is 2, 3 or 4.

7. The process according to any one of claims 1 to 5, wherein P is a non-hydrolyzable substituent.

5 8. The process according to claim 7, wherein said non-hydrolyzable substituent is an alkyl, aryl or fluoroalkyl group.

9. The process according to any one of claims 3 to 8, wherein the step e) is performed at room temperature

10 10. The process according to any one of claims 3 to 9, wherein the step is performed at a temperature in the range of 40-80 °C.

11. The process according to any one of claim 1 to 10, wherein the nitroxyl radical defined at step b) is
15 additioned at the same time of the mixture components defined at step a).

12. The process according to any one of the claims from 1 to 11, wherein the mixture whereof at step a) is prepared in a stable stock solution.

20 13. The process according to claim 12, wherein said stable stock solution is acidic.

14. The process according to claim 13, wherein said stock solution comprises tetramethoxy-orthosilane, methanol, water and HCl in a molar ratio of 1:5:4:1:7 10⁻⁴
25 respectively.

15. The process according to any one of claims 1 to 14, wherein said stable nitroxyl radical recited at step b) is substituted in 4' position with functional groups.

30 16. The process according to claim 15, wherein said functional groups are -OH, =O or -NO₂, so that said nitroxyl radical is 4-hydroxy-TEMPO, 4-oxy-TEMPO or 4-amino-TEMPO.

17. The process according to any one of claims 1 to 16, wherein said stable organic nitroxyl radical is
35 physically entrapped in the sol-gel glassy matrix.

18. The process according to claim 15 or 16, wherein said nitroxyl radical is chemically bound to an

WO 99/47258

PCT/IT99/00063

- 21 -

hydrolyzable metal precursor comprising a derivatizable group.

19. Process for the production of catalytic materials according to claim 18, wherein said chemical bond between the alkoxysilane and the nitroxyl radical is carried out by stirring a solution comprising the nitroxyl radical or the precursor of said nitroxyl radical in the alcohol corresponding to said nitroxyl radical, with an alkoxysilane, followed by the addition of water.

20. The process according to claim 18, wherein said nitroxyl radical is the 4-oxy-TEMPO and said precursor is the 3-aminopropyl-trimethoxysilane.

21. The process according to claim 18 or 20, wherein said chemical bond is obtained by stirring a solution of 4-oxy-TEMPO in methanol with an equimolar amount of the 3-aminopropyl-trimethoxysilane liquid at room temperature for three hours, said solution is added to an acidic stock solution of tetramethoxy-orthosilane in methanol and polycondensed with the addition of water.

22. The process according to any one of claims 1 to 21, wherein said catalytic materials are of a shape selected in the group comprising disc, bar, film, monolith, fibers and powder.

23. The catalytic materials obtained with a process as claimed in any one of the claims from 1 to 22.

24. A process for oxidizing an alcohol to the oxidized products thereof, characterised in that said reaction is carried out in liquid phase in presence of a catalytic material as defined in claim 23, in presence of an oxidizing agent.

25. The process according to claim 24, wherein said oxidation occurs in presence of hydrogen.

26. The oxidation process according to claim 24 or 25, wherein said oxidizing agent is selected in a group comprising an hypochlorite, an hypobromite, Cu(II), K₃Fe(CN)₆, NaBrO₂, NaNO₃, N₂O₄, Cl₂, Br₂.

WO 99/47258

PCT/IT99/00063

- 22 -

27. The oxidation process according to claim 26, wherein said oxidizing agent is Cu(I).

28. The oxidation process according to any one of claims 24 to 27, wherein said solvent is water

5 29. The oxidation process according to any one of claims 24 to 27, wherein said solvent is an organic solvent.

10 30. The oxidation process according to claim 29, wherein said organic solvent is dichloromethane, dimethylformamide, toluene and benzene.

31. The oxidation process according to any one of claims 28 to 30, wherein said alcohols are primary alcohols.

15 32. The oxidation process according to any one of claims 28 to 30, wherein said alcohols are secondary alcohols.

33. The oxidation process according to any one of from 28 to 30, wherein said alcohols are steroid, allylic alcohols, rethynol, terpens and carbohydrates.

20 34. The oxidation process according to any one of claims 24 to 33, wherein said oxidation products are carboxyl acids.

25 35. The oxidation process according to any one of claims 24 to 33, wherein said oxidation products are ketons.

36. The oxidation process according to any one of claims 24 to 33, wherein said oxidation products are aldehydes.

30 37. The oxidation process according to any one of claims 24 to 36, wherein said oxidation is carried out at an acidic pH.

38. The oxidation process according to any one of claims 24 to 36, wherein said oxidation is carried out at an alkaline pH.

35 39. The oxidation process according to any one of claims 24 to 33, wherein said oxidation is carried out at a neutral pH.

WO 99/47258

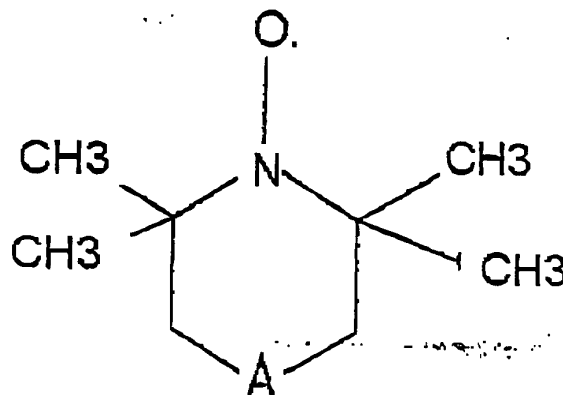
PCT/IT99/00063

- 23 -

40. The oxidation process of alcohols according to any one of the claims from 24 to 39, wherein said oxidation comprises the steps of:

- i) adding said catalytic material to a solution of said alcohol;
- ii) adding the primary oxidizing agent;
- iii) filtering the catalytic material; and
- iv) reusing the filtered catalytic material according to steps i), ii) and iii).

41. A process for the preparation of reactive sol-gel materials by the entrapment of stable nitroxyl radicals, comprising polymerizing at least one monomer of the formula $M(R)_n(P)_m$ belonging to the group of metal- or semimetal alkoxides, metal esters or semi-metal esters, where M is a semi- or a metallic element, R is an hydrolyzable substituent, n is an integer of 1 to 6, P is a non-polymerizable substituent and m is an integer of 0 to 6, under acidic, neutral or basic conditions in the presence of stable di-tertiary-alkyl nitroxyl radicals or its precursors of formula



wherein A represents a chain of preferably two or three atoms, in particular carbon atoms (methylene groups) or a combination of one or two carbon atoms with oxygen or nitrogen atom, to form a gel at room temperature, containing the said dopant trapped therein,

WO 99/47258

PCT/IT99/00063

- 24 -

5 followed by a drying step chosen among low pressure (under 70mm Hg; and preferably 15mm Hg) liophilisation to yield an areogel powder, a mild heat treatment (lower than 100° C, and preferably at 45° C) at atmospheric pressure to form a porous xerogel, coating of the gel on a mesoporous inorganic oxide (e.g. pumice stones) followed by solvent removing at low pressure (preferably at 15 mm Hg).

10 42. A process where an organic primary or secondary alcohol is dissolved in an organic solvent or in water and is oxidised in the presence of a doped material prepared as defined by claim 41, and in the presence of a primary oxidant chosen among Cu (II) salts, an hypobromite, an hypochlorite, a Cu (I) salt along with
15 oxygen bubbled through the solution.

43. A continuous process as defined in claim 2 where the oxidised product is removed while the alcoholic substrate is processed and the catalytic material is retained in the solution.

20 44. A process for the preparation of catalytic materials, a process of alcohol oxidation and a catalytic material as aforescribed.



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : B01J 31/02, 37/03, C07C 51/235	A1	(11) International Publication Number: WO 99/47258 (43) International Publication Date: 23 September 1999 (23.09.99)
<p>(21) International Application Number: PCT/IT99/00063</p> <p>(22) International Filing Date: 18 March 1999 (18.03.99)</p> <p>(30) Priority Data: RM98A000172 18 March 1998 (18.03.98) IT</p> <p>(71) Applicants (for all designated States except US): CONSIGLIO NAZIONALE DELLE RICERCHE [IT/IT]; Piazzale Aldo Moro, 7, I-00185 Roma (IT). YISSUM RESEARCH DEVELOPMENT COMPANY OF THE HEBREW UNIVERSITY OF JERUSALEM [IL/IL]; P.O. Box 4279, 91042 Jerusalem (IL).</p> <p>(72) Inventors; and (75) Inventors/Applicants (for US only): <u>PAGLIARO</u>, Mario [IT/IT]; Viale del Fante, 50, I-90146 Palermo (IT). <u>AVNIR</u>, David [IL/IL]; Novomiesky Street 2, 96908 Jerusalem (IL). <u>DEGANELLO</u>, Giulio [IT/IT]; Via Messina, 3, I-90141 Palermo (IT). <u>BLUM</u>, Jochanan [IL/IL]; Hameshoreret Rachel Street 13, 96348 Jerusalem (IL).</p> <p>(74) Agents: BAZZICHELLI, Alfredo et al.; Società Italiana Brevetti S.p.A., Piazza di Pietra, 39, I-00186 Roma (IT).</p>		<p>(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).</p> <p>Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p>
<p>(54) Title: CATALYTIC MATERIALS FOR SELECTIVE OXIDATION OF ALCOHOLS, PROCESS FOR PRODUCTION THEREOF AND THEIR USE IN ALCOHOL OXIDATION PROCESS</p>		
<p>(57) Abstract</p> <p>A versatile methodology to obtain efficient catalytic materials suitable for selective, liquid-phase oxidations of alcohols is described. Solid inorganic membranes were prepared by the sol-gel procedure by adding a solution of stable organic nitroxyl radicals at the onset of the polymerization of silicon alkoxide monomers. In this way, micro- and mesoporous materials can be obtained that are effective and recyclable catalytic mediators for highly selective oxidations of a vast class of primary and secondary alcohols carried out with several primary oxidants. Delicate substrates such as carbohydrates and allylic alcohols can selectively be oxidised with these novel catalytic materials.</p>		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

CATALYTIC MATERIALS FOR SELECTIVE OXIDATION OF ALCOHOLS,
PROCESS FOR PRODUCTION THEREOF AND THEIR USE IN ALCOHOL
OXIDATION PROCESS

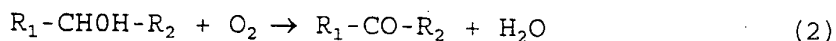
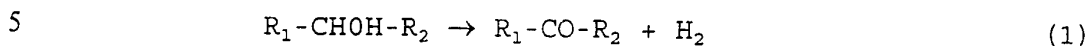
DESCRIPTION

5 Background and previous knowledge

Most (>90%) of the industrial chemical processes are catalytic [J.M. Thomas, W.J. Thomas, Principles and Practice of Heterogeneous Catalysis, VCFL Weinheim, 1997]. Of these, a percentage higher than 75% makes use of heterogeneous catalysts [J.H. Clark, Catalysis of Organic Reactions by Supported Inorganic Reagents, VCH, Weinheim, 1994]. Heterogeneous catalysts are widely used in the petrochemical industry in several chemical processes including hydrocarbon cracking (on zeolites),
10 olefin hydrogenations (on precious metals) and stereospecific polymerizations [J.H. Clark, Catalysis of Organic Reactions by Supported Inorganic Reagents, VCH, Weinheim, 1994]. On the other hand, many of the chemical synthesis of interest to the pharmaceutical and secondary
15 chemical industries are liquid-phase homogeneous catalytic or stoichiometric processes [G. Sironi, La Chim. and l'Ind., 79 (1997) 1173-1177; M. Hudlicky Oxidations in Organic Chemistry, Acs Monograph, No. 186, 1990]. The interest is high in converting homogeneous
20 processes into efficient and clean heterogeneous catalytic conversions. The oxidation of alcohols to carbonyl derivatives is a typical fine chemical production process in need for such conversion [G. Sironi, La Chim. and l'Ind., 79 (1997) 1173-1177]. Due to
25 the urgent demand of new oxidative technologies mentioned above, very recently Sheldon and colleagues were terming "philosophers' stones" efficient heterogeneous catalysts for liquid-phase oxidations in widely known international publication [R.A. Sheldon, m, Wallau, I.W.C.E. Arends, U.
30 Schuchardt, Acc. Chem. Res., 31 (1998) 485-493]. Apart from industrial, large-scale high temperature (600°C) catalytic dehydrogenations (equation 1) and oxidative

- 2 -

dehydrogenations (equation 2) carried out on Ag and Cu catalysts [M. Muhler in: Handbook of Heterogeneous Catalysis, VCH, Weinheim, 1997],



alcohol oxidations are carried out with stoichiometric amounts of oxidants (periodinanes, Dess-Martin reagent, chromium and manganese salts, mineral acids) or by electrochemical reactions. Environmental, economical and technological reasons make of primary importance the substitution of these homogeneous processes with heterogeneous catalytic oxidations carried out with clean oxidants such as O_2 , HO_2O_2 or hypochlorite [J.A. Cusumano, J. Chem. Ed., 72 (1995) 959-964]. In general, however, the selectivity required in fine chemicals production is much higher as compared to that of classical large-scale heterogeneous catalysis.

Traditionally, heterogeneous catalysts are obtained by supporting the active species onto an inert solid of high surface area (silica, celite, carbon, alumina, clays etc.) in order to maximise the dispersion of the active species. The solid carrier can be an inorganic oxide or an organic polymer. Phase separation between the catalytic species and the reagents in the reaction mixture permits the facile separation of the catalyst and - in principle - either to reuse the catalyst in a subsequent reaction or its employment in a continuous process in which the reaction product is separated while the reactant is processed. Typically, heterogeneous catalysts are prepared by impregnation of the inorganic support with a solution of the active species (i.e. metals ions) or by derivatising the surface of the solid in a heterogeneous reaction between the surface reactive groups (hydroxyl) and an organoderivate of the catalytic molecule.

- 3 -

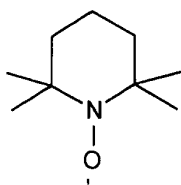
Few mild catalytic oxidative processes are available. Catalysts of platinum and palladium supported on carbon are used at room temperature for alcohol oxidative dehydrogenation (equation 2) in batch reactors containing a suspension of the catalyst particles in a solution of the alcohol through which air is bubbled. The mild reaction conditions make it possible to oxidise sensitive compounds including carbohydrates [M. Besson, F. Lahmer, P. Gallezot, P. Fuertes, G. Flèche, J. Catal, 152 (1995) 116-122] and steroids, [T. Akihisa et al., Bull. Chem. Soc. Jpn. 59 (1986) 680-685], but reaction conditions need to be strictly controlled in order to avoid substrate overoxidation and rapid catalyst deactivation (by metal particles oxidation, sintering etc.). An efficient commercial oxidation catalyst is the inorganic oxide titanium silicalite (TS-1) used with aqueous H_2O_2 (30% w/w) for the catalytic oxidation of primary and secondary alcohols as described in [R. Murugawel. H.W. Roesky, Angew Chem. Int. Ed. Engl., 36 (1997) 477-479]. Selectivity of TS-1, however, is not high and different oxidisable groups such as double bonds and primary or secondary alcohol groups in a substrate are all rapidly oxidised as well.

There exists high demand of new, selective and efficient catalysts of oxidative processes and intense research efforts are devoted towards this aim both in industrial and in academic laboratories world-wide. Recently for instance, a new aerobic selective oxidative process has been described which uses diazo complexes of Cu (I) supported on K_2CO_3 . Alcohols dissolved in apolar organic solvent can be dehydrogenated into carbonyl compounds by using oxygen contained in air as primary oxidant [I.E. Markó, P.R. Giles, M. Tsukazaki, S.M. Brown, C.J. Urch, Science, 274 (1996) 2044-2046]. Reactions temperatures employed are high (70-90°C) and - due to low surface area of the inorganic support - an excess of K_2CO_3 (2 equiv.) is needed for optimum

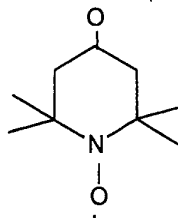
- 4 -

catalytic activity. The Authors therefore suggest the use of di-*t*-but-azodicarboxylate (DBAD) as a better primary oxidant affording less carbonate burden (10% equiv.) [I.E. Markó, P.R. Giles, M. Tsukazaki, S.M. Brown, C.J. Urch, *Angew. Chem. Int. Ed. Engl.*, 36 (1997) 2208-2210]. Another novel catalytic reaction system has been introduced in Japan where alcohols are oxidised with 30% H₂O₂ in the presence of catalytic tungsten complexes with high turnover numbers [R. Nogori, K. Sato, M. Aoki, J. Takahi, *J. Am. Chem. Soc.*, 119 (1997) 12386-12390].

Highly promising candidates suitable for the preparation of efficient heterogeneous catalysts may originate from stable organic nitroxyl radicals. These are di-tertiary-alkyl nitroxyl radicals (Figure 1) with A representing a chain of two or three atoms (methylene groups) or a combination of one or two atoms with an oxygen or nitrogen atom as described in International patent application PCT/NL94/00217. Typically, the preferred radicals employed belong to the family of the 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO, 1) and its derivatives substituted in position 4 (4-oxo-TEMPO, 2).



1

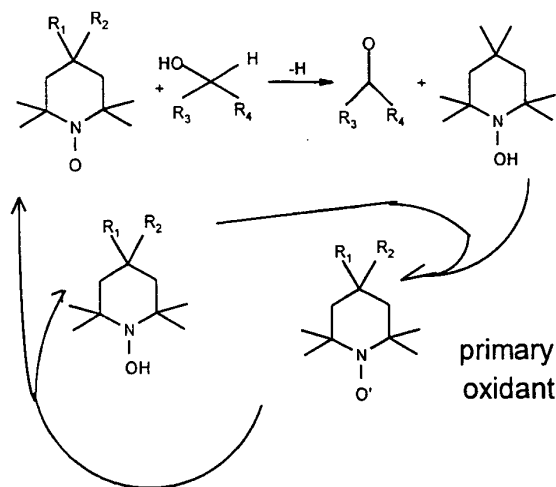


2

These species are highly efficient and versatile catalysts suitable for highly selective oxidation of hydroxyl containing compounds either to carbonyl or to carboxyl compounds, depending on applied reaction conditions. Their use as catalytic mediators in alcohol oxidations has been recently reviewed in depth in [A.E.J.

- 5 -

de Nooy, A.C. Besemer, H. van Bekkum, Synthesis, (1996) 1153-1174]. Reactions can be carried out both at acidic and alkaline pH's with important difference in the selectivity observed. Furthermore, the oxidation reaction can be performed in different reaction media, i.e. in organic solvent, in biphasic water-organic solvent system and in water. In these catalytic oxidations, the active species (oxidant) is the (cyclic) nitrosonium ion which is generated *in situ* by adding an active primary oxidant including, among the others, Cu (II), NaOCl, NaOBr, NaBrO₂, N₂O₄, K₃Fe(CN)₆. It is believed that positive nitrogen of the cyclic nitrosonium ion attacks the alcoholic oxygen, with subsequent hydride abstraction in a bielectronic oxidative step involving carbonyl formation and acid release in the reaction mixture.

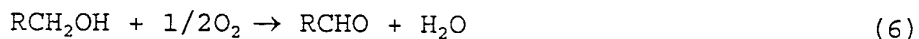
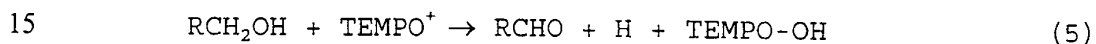
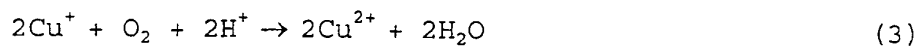


The hydroxylamine formed in the oxidative step disproportionates with the free radical to yield the nitrosonium ion or is directly oxidised with the primary oxidant to nitrosonium ion in a bielectronic reaction. As stated above, several alcoholic substrates can be oxidised at completion with high reaction rate and remarkable selectivity (compatibility with other oxidisable groups) and while alcohol oxidation in organic

- 6 -

solvent stops at the first stage yielding a carbonyl compound, in H₂O the oxidation proceeds through a second oxidative step to yield a carboxylic acid.

5 In organic solvent containing up to 5% of H₂O air can be used as stoichiometric oxidant by adding a catalytic amount of Cu (I) so that, for instance, alcohols containing highly sensitive heterocyclic substitutes can be selectively oxidised (equation 6) into the corresponding carbonyl compound and no base has to be
10 used to take up the acid formed in the oxidative step (equation 5),



Remarkably, with the CuCl/O₂ system as primary oxidant, oxidation of allylic and benzylic alcohols
20 proceeds smoothly even at -70 °C [M.F. Semmelhack, C.R. Schmid, D.A. Cortés, C.S. Chou, J. Am. Chem. Soc., 106 (1984) 3374-3376], The simplicity and effectiveness of this molecular aerobic oxidation should be compared to Cu (I) mediated aerobic oxidations [L. Prati, N. Ravasio, M.
25 Rossi, La Chim. and L'Ind., 79 (1997) 189-196]. In these latter reactions, including that recently developed by Zeneca [I.E. Markó, P.R. Giles, M. Tsukazaki, S.M. Brown, C.J. Urch, Science, 274 (1996) 2044-2046] or in enzymatic process recently developed [P. Chaudhuri, M. Hess, U.
30 Flörke, K. Wieghardt, Angew. Chem., 110 (1998) 2340-2343], hydrogen transfer takes place between the alcoholic substrate and O₂, that are both complexed to Cu (I) metal center. On the other hand, in TEMPO mediated oxidations, the oxidant is the cyclic nitrosonium ion and
35 the only function of dissolved catalytic amount of Cu (I) is in forming the oxidant Cu (II) by splitting O₂ in a catalytic reaction cycle.

- 7 -

In the carbohydrate industry, oxidation is a useful means to obtain products of high added value starting from low cost, non toxic and readily available materials [K. van der Wiele, Carbohydrates in Europe, 13 (1995) 3].

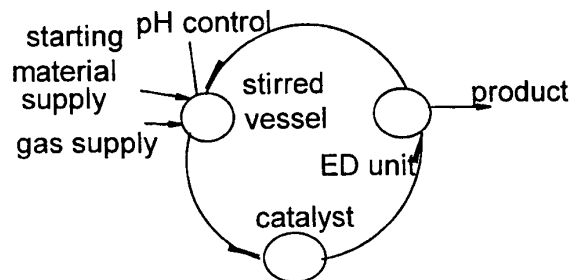
5 Mono-oxidised sugars are the products of commercial interest but, due to the chemical similarity of different alcoholic groups in sugars, the selectivity of most chemical oxidants is low. Thus, often protection-deprotection steps of different oxidisable hydroxyls are

10 required before and after the chemical oxidative step, as in the case of the commercial production of ascorbic acid (vitamin C) from a sorbose derivative. Accordingly, the introduction of new selective catalytic processes to substitute the traditional stoichiometric oxidations is

15 the object of intense research efforts. New stable bimetallic (Pd-Bi/C) catalysts have been recently introduced for the preparation of mono-oxidised sugars; the catalyst Palatinose® (Pt/C) is used in an efficient, continuous catalytic process for the oxidation of D-

20 glucose to D-gluconate. in which air is bubbled in an aqueous glucose solution and the reaction product is separated by electrophoresis while the sugar is continuously processed [M. Kunz et al., German patent DE OS 43 07 388 A1]

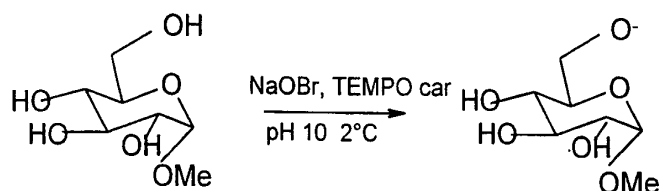
25



In contrast to D-gluconic acid, D-glucuronic acid is not produced on an industrial scale despite its

- 8 -

considerable importance [M. Boiret, A. Marty, J. Chem. Ed., 63 (1986) 1009-1011]. Its synthesis on a small scale is carried out with an enzyme and the price of the resulting compound is high. Moreover, native carbohydrate polymer containing carboxylic group at C-6 (polyuronates) find many commercial applications due to their remarkable properties as complexing agents and for abilities to form gels at low-concentrations (hyaluronanes, pectins, xanthan etc). A major breakthrough in the commercially relevant field of carbohydrate oxidations occurred therefore with the introduction of the regioselective homogeneous oxidation of carbohydrate primary alcohols into carboxylic acids mediated by nitroxyl radicals as described in PCT/NL94/00217. By using NaOBr as stoichiometric oxidant together with a catalytic amount of the radical 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) at alkaline pH (10) and low temperature (2° C), sugars protected at the anomeric center are rapidly and selectively converted into respective uronates,



Due to a cyclic reaction mechanism, this alkaline oxidation method affords the rapid (80 min) regioselective primary alcohols oxidation of soluble polymeric carbohydrates (i.e. starch, inulin, pullulan) affording highly valuable and pure solution of the corresponding polyuronate. The use of NaOBr in place of NaOCl significantly increases the reaction rate. At pH 10 reaction rate is fastest while the non-selective oxidation of sugars by hypohalite has a much lower reaction rate and no side products are detected apart from the uronate. A recent comparative study clearly

- 9 -

demonstrated the superiority of glucose oxidation mediated by TEMPO as compared to its oxidative dehydrogenation on Pt/C [K. Li, R. F. Helm, Carbohydr. Res., 273 (1995) 249-255]. Another comparative cost analysis comparing TEMPO (with CuCl/air as stoichiometric oxidant) mediated oxidation with several stoichiometric oxidation protocols including the Swern's method (DMSO, oxalyl chloride) clearly supports the choice of the former as optimal method for fine alcohol oxidations [K, Dean Bowles, D.A. Quincy, J.I. McKenna, N.R. Natale, J. Chem. Ed., 63 (1986) 358-360]. The analysis took in consideration the expense of solvents and was based on 5 mol% as the amount of free radical needed for obtaining reasonable yields. A further advantage was found in the ease of upscaling of the method. It should be noted that the use of O₂ as the primary oxidant (and consequent formation of H₂O as unique by-product) along with the low toxicity of the radicals are ideal intrinsic characteristics of the method from both environmental and safety viewpoints.

The versatility of alcohol oxidation mediated by nitroxyl radicals makes their use attractive to diverse industries. Accordingly, several homogeneous oxidative processes mediated by nitroxyl radicals have been patented and are commercially being used for the production of fine chemicals, including high yield (91.6%) E-retinol oxidation to E-retinal with CuCl/O₂ in DMF [G.H. Knaus, J. Paust, German patent 3.705 785], the above mentioned alkaline regioselective oxidation of carbohydrate in water [PCT/NL94/00217], and the oxidation of alkyl polyglucosides (APG's) and several long chain alcohols (German patent DE 4209 869). Since nitroxyl radicals are costly (~10 \$/g on a small scale, Aldrich catalogue 1999) and moderately toxic [T.S. Straub, J. Chem. Ed., 68 (1991) 1048-1049], their recovery would be desirable. Immobilization of the radicals on solid supports would facilitate their separation from the

- 10 -

reaction mixture.

Few immobilization procedures have been reported and, with a single exception reported below, all concern organic polymers. A copolymerisation of an organic monomer containing a TEMPO precursor has been described in which the TEMPO precursor fragments are polymerised and then converted to TEMPO fragments [T. Miyazawa, T. Endo, M. Okawara, J. Polym. Sci., Polym. Chem. Ed., 23 (1985) 1527-1535]. Similarly, 4-amino-TEMPO has been immobilized on poly(acrylic acid) and the resulting polymer was subsequently coated on a glassy electrode [T. Osa et al., Chem. Lett., (1988) 1423-1428]. In the carbohydrate field, especially aiming at pharmaceutical and food applications, the preparation of heterogeneous catalysts of immobilised nitroxyl radicals has been recently attempted. The reductive amination of the keto 4-oxo-TEMPO function by adding its solution in MeOH to a suspension of an amino-silica (Bio Sil NH₂ 90 15-35, Bio Rad), was followed by a reduction step with NaBH₃CN as described in International patent application [PCT/NL96/00201]. As stated in the cited review it remains to be shown that the immobilized radicals are stable after frequent use and longer periods of time [A.E.J. de Nooy, A.C. Besemer, H. van Bekkum, Synthesis, (1996) 1153-1174]. Thus, for instance the catalytic activity of the material thereby obtained was tested in the oxidation of anomERICALLY protected D-glucose; upon 3 consecutive runs the material had lost its catalytic properties while reaction rate was considerably lower than corresponding homogenous reaction [A. Heeres, H. van Doren, K.F. Gotlieb, I.P. Bleeker, Carbohydr. Res., 299 (1997) 221-227]. The Authors concluded that azeotropic distillation is the method of choice for the recovery of TEMPO [PCT/NL96/00201].

35 Description of the invention

The present invention describes the preparation of efficient and recyclable catalytic materials obtained

- 11 -

supporting stable nitroxyl radicals in a solid, inert matrix by the sol-gel [C.F. Brinker, G.W. Scherer, Sol-gel Science, Academic Press, San Diego]. In fact the sol-gel technology allows to dope the glasses obtained through the polymerization (catalysed by acid or base) of metal alkoxides (or their hydrolysis products) in water with any kind of organic molecule by adding a solution of the doping substance at the onset of polymerization [D. Avnir, M. Ottolenghi, S. Braun, R. Zusman, US Patent 5,292,801 (1994)]. The materials obtained in this way are porous glassy oxides with surface areas of up to hundreds of m^2/g and narrow pores with diameters between 0.5 and 500 nm. The doped porous glasses show unique properties. Thus, i) the entrapped molecules retain their physical and chemical properties and, ii) are accessible to external reagents through the pore network. Moreover, iii) the inorganic matrix is chemically and thermally inert and iv) the entrapped molecules show enhanced stability [D. Avnir, D. Levy, R. Reisfeld, I Phys. Chem., 88 (1984) 5956-5959]. Because the sol-gel matrix is a high surface area absorbent which concentrates the reagents, often the reactions with the dopant have shown enhanced selectivity and sensitivity compared to the corresponding homogeneous reactions [O. Lev, M. Tsionski, L. Rabinovich, V. Glezer, S. Sampath, I. Pankratov, J. Gun, Anal. Chem., 67 (1995) 22A-30A].

In contrast with organic polymer supports, the ceramic sol gel supports are superior in their thermal stability, inertness towards the entrapped species, protectability of the entrapped molecule, and in their porosity and high surface area. Nitroxyl radical immobilization by the sol-gel method was carried out in order similarly to Lev [A. Shames, O. Lev, B. Iosefzon-Kuyavskaya, J. Non-Cryst. Solids 175 (1994) 14-20] and to [K. Matsui, T. Kaneko, Y. Yaginuma, M. Ryu, J. Sol-Gel Sci. Tech. 9 (1997) 273-277], both of which did not recognize the reactivity properties of the final doped

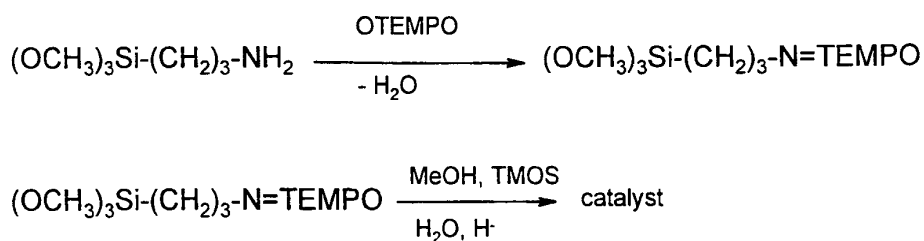
- 12 -

xerogel. The cited [A. Heeres, H. van Doren, K.F. Gottlieb, I.P. Bleeker, Carbohydr. Res., 299 (1997) 221-227] surface derivatization procedure required several synthetic steps and resulted in a material whose catalytic activity deteriorated rapidly upon 3 consecutive oxidative runs. Indeed, we emphasize here the major difference between surface derivatization and entrapment in sol-gel materials: while the former requires the formation of a new covalent bond, and leaves the anchored molecule unprotected at the pore surface, the entrapment in sol-gel materials is physical in nature requiring no chemical step of covalent bonding, and highly protects the entrapped molecule within the surrounding cage of the ceramic material. An intermediate situation in which an amine function is for covalent bonding is added for anchoring the nitroxyl radical and for distributing it within the supporting matrix by the sol-gel procedure is also described and claimed below. Furthermore, we prepared mesoporous catalytic materials by i) coating the surface of an inorganic mesoporous inorganic oxide (e.g. pumice stones), and ii) by the preparation of areogels in place of above mentioned xerogels by removing the solvent under reduced pressure (15mm Hg; liophilisation) as described in [N. Huesing, U. Schubert, Angew. Chem, Int. Ed. Engl., 37 (1998) 22-45].

The non-obvious novelty here is that when entrapped in a sol-gel glassy matrix, an active radical is not quenched but retains its characteristic oxidative properties. It is further non obvious that such entrapped oxidant exhibits high selectivity in alcohols oxidation as reported below; none of the doped catalysts leaches out while being accessible for reaction and that catalysts are recyclable. All of these properties are of major interest and relevance to the carbohydrate industry, and, in fact, to all industrial processes where an alcohol is to be oxidised. Porous silica sol-gel glasses were prepared which contain nitroxyl radicals

- 13 -

both physically and chemically entrapped. Physical entrapment was carried out with TEMPO by adding the oxidant to the initial polymerizing mixture. Covalent entrapment was conducted by mixing 3-aminopropyl trimethoxysilane [NH₂-CH₂CH₂CH₂-Si(OCH₃)₃] with a solution of 4-oxo-TEMPO in methanol followed by reduction of the immine thereby formed. The precursor monomer is further polymerized with tetramethoxyorthosilicate (TMOS) according to the sol-gel procedure.



The polycondensation of alkoxysilanes is associated with gelation of the sol, which after drying is densified by mild heat treatment to form a porous glass. The properties of the final glass are determined by the chemical and physical conditions during the preparation process. They depend upon the ratio metal/water (r), the amount of added alcohol, the alkoxide, the pH, the type of the acid/base catalyst, the temperature, the drying time and the amounts of added organic additives such as surfactants. Pore size and surface area are controlled by variations of all of these parameters. Hence, selection of optimal parameters is an important aspect of this invention. The following description of experiments are typical examples for such optimal procedures, but they are given without losing generality from the point of view of variations in these procedures which are obvious to the person skilled in the field.

30 EXAMPLES

Preparation of sol-gel glasses doped with nitroxyl radicals was conducted as follows.

- 14 -

Example 1

Sol-gel glasses physically doped with nitroxyl radical.

5 A standard mixture for the physical sol-gel glasses entrapment of TEMPO contained tetramethoxyorthosilicate (TMOS) (2.95 mL), H₂O (1.0 mL) and MeOH (2mL). The catalyst HCl (10³ M, 1.0 mL) and 50 mg TEMPO, dissolved in methanol (2 mL), were added to the hydrolyzed TMOS solution. Gelation took place after approximately 2 hours
10 in glass vessels covered with an aluminum foil and the gels were then aged for 4 days at ambient temperature. Final drying was affected in an incubator oven at 50° C for 6 days, reaching constant weight This procedure yields glasses doped with TEMPO in any desired shape and
15 form (discs, rods, granules, powders, films etc.). The procedure described yielded a monolithic glass which was crushed in granules.

Example 2

20 Sol-gel glasses chemically doped with nitroxyl radical.

The chemical entrapment of the nitroxyl radicals was carried out in 2 steps. The catalyst is prepared by anchoring the nitroxyl radical through the oxo group of 4-oxo-TEMPO to the amino group of
25 aminopropyltrimethoxysilane and further polymerizing the resulting monomer with an acidic sol of tetramethoxyortosilicate (TMOS, Si(OCH₃)₄). After 24h stirring a solution of 4-oxo-TEMPO (424 mg) in methanol (3 mL) with aminopropyltrimethoxysilane (H₂N-(CH₂)₃-
30 Si(OCH₃)₃, 480 mL, 10% molar excess) the resulting alcoholic immine is mixed with a portion of acidic sol stock TMOS solution previously prepared by mixing TMOS (29,5 mL), H₂O (3.6 mL), MeOH (32,40 mL) and HCl IN (140 µL). Thus, a portion of the sol stock mixture (3.28 mL)
35 was partially neutralized with NH₄OH 0.1 M (69.8 µL) and mixed together with 1.14 mL of the immine precursor solution. Methanol (7.41 mL) was subsequently added under

- 15 -

stirring followed by H₂O (3.88 mL) to promote hydrolysis and condensation. As a formal acidity measure, pH (6.0) refers to the concentration of hydrogen ions in the total. volume. The resulting mixture
5 (Si:H₂O:MeOH=1:5.5:6) gelled rapidly (10 min) in a transparent, elastic alcogel coloured in orange which was left at ambient temperature for 3 days and subsequently dried at 50° C resulting in a monolithic doped xerogel of 0.93 g. The sol described above was dried by removing the
10 solvent under reduced pressure (15mm Hg) affording an orange areogel powder.

Example 3

Chemical entrapment.

Sol-gel glasses doped with OTEMPO.

15 The chemical entrapment of the nitroxyl radicals is carried out in two stages.

Usually, a sol stock solution contains TMOS, MeOH, H₂O and HCl, remaining stable for months. Thereafter, a solution containing a chemically bound TEMPO precursor is
20 prepared.

An OTEMPO solution is stirred in methanol with tri-amino-propyl tri-methoxy-silane (for 2 hours at 20°C). Typically, 4 ml of the sol stock solution containing TMOS, MeOH, H₂O and HCl (7×10^{-5} molar) with a molar
25 ratio of $1:5:4:1:7 \times 10^{-4}$ (J. Brinker's procedure, Sandia, Sandia National Labs, US) are added with a 60 mg OTEMPO solution in methanol (2.45 ml) and tri-amino-propyl tri-methoxy-silane (1.64 ml) with a subsequent adding of H₂O (1.7 ml). Gelification occurs in a few
30 minutes. Then the gel is dried in an incubator at 50°C covered with a tinfoil. The resulting xerogel (dried gel) contains nitroxyl radicals that are chemically bound to the silica matrix by an immine group that can be easily reduced with NaBH₃CN. As in the previous procedure, in
35 this case as well the glasses can be obtained in any desired shape.

In the oxidative procedure the oxidized substrate is

- 16 -

isolated, while the nitroxyl radical is recovered and recycled, thanks to the catalyst heterogenous nature.

Example 4.

5 Mesoporous inorganic carriers coated with sol-gel doped films.

The sol described above in Examples 2 and 3 containing nitroxyl radicals chemically linked was used to coat the surface of an inorganic mesoporous inorganic oxide (pumice stones from the Lipari island (Italy))
10 leaving the sol in contact with the support for about 5 hours and removing the solvent under reduced pressure (15mm Hg) as described in International patent application PCT 0 832 561 AZ.

Example 5

15 Catalytic activity in the nitroxyl radicals entrapped in sol gel glasses.

Typical procedure:

The reactions of catalytic oxidation are carried out adding granules of the doped materials (e.g. 0.247 g of a catalyst 3.70% (w/w) in TEMPO, or 0.352 g of a catalyst 3.24% (w/w) in 4-oxo-TEMPO) to an aqueous solution of methyl- α -D-glucopyranoside (MGP, 1.0 g and 0.10 g of sodium bromide in 200 mL H₂O at 4 °C. A cold hypochlorite solution (10 mL, 10% w/w) previously brought to pH 10 by
20 adding 4M HCl is then added at once. The pH is followed and kept constant at 10 by adding 0.5M NaOH to the mixture reaction in order to neutralize the acid released during the reaction (Diagram I). When the oxidation is completed (no more acid formation, typically 40 min) the
25 reaction mixture is quenched by adding 96% ethanol (4mL) and by changing the pH to 6 by addition of 4M HCl. The catalyst is filtered, and the product, sodium methyl- α -D-glucopyranoside uronate is obtained from the filtrate by freeze-drying in a lyophilizer. The yield of the reaction
30 is practically quantitative. For the next reaction cycle, the catalyst is washed with cold water and reused as such under the same conditions described above.

- 17 -

Example 6

The catalytic activity of the sol-gel materials doped with nitroxyl radical thus far described was tested in different oxidative runs using α -D-methylglucopyranoside and trans-cinnamyl alcohol as substrates along with aqueous hypobromite and CuCl/air as primary oxidants, respectively. In a typical sugar oxidation the catalytic oxidation reaction was carried out by adding granules of the doped materials (e.g. 0.247 g of a catalyst 3.70% (w/w) in TEMPO, or 0.352 g of a catalyst 3.24% (w/w) in 4-oxo-TEMPO) to an aqueous, solution of methyl- α -D-glucopyranoside (MGP, 1.0 g) and sodium bromide (0.10 g) in 200 mL H₂O at 4° C. A cold hypochlorite solution (10 mL, 10% w/w) previously brought to pH 10 by adding 4M HCl, was then added at once. The pH was kept constant at 10 by adding 0.5M NaOH in order to neutralize the acid released during the reaction. When the oxidation was completed (no more acid formation, typically 40 min), the reaction mixture was quenched by adding 96% ethanol (4 mL) and by changing the pH to 6 by addition of 4M HCl. The catalyst was filtered, and the product (sodium methyl- α -D-glucopyranosiduronate) was obtained from the filtrate by freeze-drying in a lyophilizer. The yield of the reaction was practically quantitative. For the next reaction cycle, the catalyst was washed with cold water and reused as such under the same conditions described above. The catalyst was reused in 3 subsequent similar oxidation runs of the same substrate MGP with minor decrease in activity. The elemental analysis after oxidative runs did not detect any nitrogen, thus establishing the lack of leaching of the entrapped nitroxyl radicals in the reaction solution.

Example 7

Leaching, recyclability and selectivity.

The catalyst is reused in 5 subsequent similar oxidation runs of the same substrate MGP with no decrease in yield or activity.

- 18 -

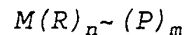
The spectra NMR cannot detect any secondary product, with the exception of the desired sodium methyl- α -D-glucopyranoside uronate. The elemental analysis after each of the four consecutive oxidative runs does not
5 detect any nitrogen, thus establishing the lack of leaching of the nitroxyl radicals entrapped in the reaction solution. It is interesting that no induction time whatsoever is observed in the subsequent oxidation runs carried out in the heterogeneous oxidation system,
10 compared to the 15 minutes in the corresponding homogenous reaction carried out with the TEMPO solution.

- 19 -

CLAIMS

1. A process for the preparation of catalytic materials for the oxidation of alcohols by means of entrapment of stable nitroxyl radicals in sol-gel glassy matrixes, characterised in that it comprises the steps of:

a) preparing a polymerizing mixture comprising at least a monomer of the formula



wherein M is a semi- or a metal element,

R is a hydrolyzable substituent

n is an integer of 1 to 6,

P is a non-polymerizable substituent, and

m is an integer of 0 to 6;

water and an alcohol promoting the mixability of said monomer with the water;

b) additioning to said mixture a stable organic nitroxyl radical selected from the group comprising the 2,2,6,6,-piperidin-1-oxyl, also denominated TEMPO, the precursors and derivatives;

c) additioning water to the said mixture; and

d) hydrolize and polycondense the monomers defined at step a) to obtain a gel.

2. The process according to claim 1, wherein in the step c) a catalyst is additioned.

3. The process according to claim 1 or 2, further comprising the steps of

e) curing said gel at a temperature lower than 200°C in order to promote the complete polycondensation, solvent evaporation and the obtaining of a dry gel, also denominated xerogel; and

f) drying said xerogel by a mild thermal treatment performed at a temperature lower than 200°C.

4. The process according to any one of claims 1 to 3, wherein M is Si, Ti, Pb or Al.

5. The process according to any one of claims 1 to 5, wherein R is an alcoxy or arylalcoxy group.

- 20 -

6. The process according to any one of claims 1 to 5, wherein n is 2, 3 or 4.

7. The process according to any one of claims 1 to 5, wherein P is a non-hydrolyzable substituent.

5 8. The process according to claim 7, wherein said non-hydrolyzable substituent is an alkyl, aryl or fluoroalkyl group.

9. The process according to any one of claims 3 to 8, wherein the step e) is performed at room temperature

10 10. The process according to any one of claims 3 to 9, wherein the step is performed at a temperature in the range of 40-80 °C.

11. The process according to any one of claim 1 to 10, wherein the nitroxyl radical defined at step b) is
15 additioned at the same time of the mixture components defined at step a).

12. The process according to any one of the claims from 1 to 11, wherein the mixture whereof at step a) is prepared in a stable stock solution.

20 13. The process according to claim 12, wherein said stable stock solution is acidic.

14. The process according to claim 13, wherein said stock solution comprises tetramethoxy-orthosilane, methanol, water and HCl in a molar ratio of 1:5:4:1:7 10⁴
25 respectively.

15. The process according to any one of claims 1 to 14, wherein said stable nitroxyl radical recited at step b) is substituted in 4' position with functional groups.

30 16. The process according to claim 15, wherein said functional groups are -OH, =O or -NO₂ so that said nitroxyl radical is 4-hydroxy-TEMPO, 4-oxy-TEMPO or 4-amino-TEMPO.

17. The process according to any one of claims 1 to 16, wherein said stable organic nitroxyl radical is
35 physically entrapped in the sol-gel glassy matrix.

18. The process according to claim 15 or 16, wherein said nitroxyl radical is chemically bound to an

- 21 -

hydrolyzable metal precursor comprising a derivatizable group.

19. Process for the production of catalytic materials according to claim 18, wherein said chemical
5 bond between the alkoxysilane and the nitroxyl radical is carried out by stirring a solution comprising the nitroxyl radical or the precursor of said nitroxyl radical in the alcohol corresponding to said nitroxyl radical, with an alkoxysilane, followed by the addition
10 of water.

20. The process according to claim 18, wherein said nitroxyl radical is the 4-oxy-TEMPO and said precursor is the 3-aminopropyl-trimethoxysilane.

21. The process according to claim 18 or 20, wherein
15 said chemical bond is obtained by stirring a solution of 4-oxy-TEMPO in methanol with an equimolar amount of the 3-aminopropyl-trimethoxysilane liquid at room temperature for three hours, said solution is additioned to an acidic stock solution of tetramethoxy-orthosilane in methanol
20 and polycondensed with the addition of water.

22. The process according to any one of claims 1 to 21, wherein said catalytic materials are of a shape selected in the group comprising disc, bar, film, monolith, fibers and powder.

23. The catalytic materials obtained with a process
25 as claimed in any one of the claims from 1 to 22.

24. A process for oxidizing an alcohol to the oxidized products thereof, characterised in that said reaction is carried out in liquid phase in presence of a catalytic
30 material as defined in claim 23, in presence of an oxidizing agent.

25. The process according to claim 24, wherein said oxidation occurs in presence of hydrogen.

26. The oxidation process according to claim 24 or
35 25, wherein said oxidizing agent is selected in a group comprising an hypochlorite, an hypobromite, Cu(II), K₃Fe(CN)₆, NaBrO₂, NaNO₃, N₂O₄, Cl₂, Br₂.

- 22 -

27. The oxidation process according to claim 26, wherein said oxidizing agent is Cu(I).

28. The oxidation process according to any one of claims 24 to 27, wherein said solvent is water

5 29. The oxidation process according to any one of claims 24 to 27, wherein said solvent is an organic solvent.

30. The oxidation process according to claim 29, wherein said organic solvent is dichloromethane, dimethylformamide, toluene and benzene.

31. The oxidation process according to any one of claims 28 to 30, wherein said alcohols are primary alcohols.

32. The oxidation process according to any one of claims 28 to 30, wherein said alcohols are secondary alcohols.

33. The oxidation process according to any one of from 28 to 30, wherein said alcohols are steroid, allylic alcohols, rethynol, terpens and carbohydrates.

34. The oxidation process according to any one of claims 24 to 33, wherein said oxidation products are carboxyl acids.

35. The oxidation process according to any one of claims 24 to 33, wherein said oxidation products are ketons.

36. The oxidation process according to any one of claims 24 to 33, wherein said oxidation products are aldehydes.

37. The oxidation process according to any one of claims 24 to 36, wherein said oxidation is carried out at an acidic pH.

38. The oxidation process according to any one of claims 24 to 36, wherein said oxidation is carried out at an alkaline pH.

39. The oxidation process according to any one of claims 24 to 33, wherein said oxidation is carried out at a neutral pH.

- 23 -

40. The oxidation process of alcohols according to any one of the claims from 24 to 39, wherein said oxidation comprises the steps of:

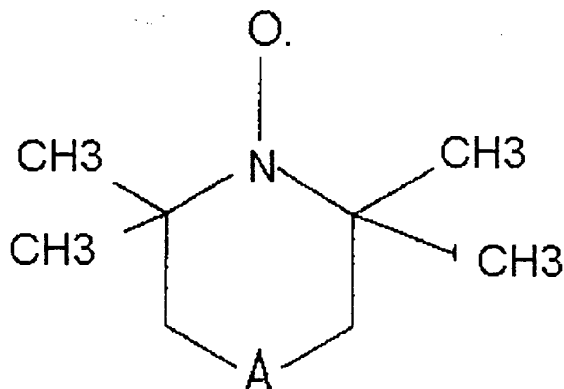
i) adding said catalytic material to a solution of said alcohol;

ii) adding the primary oxidizing agent;

iii) filtering the catalytic material; and

iv) reusing the filtered catalytic material according to steps i), ii) and iii).

41. A process for the preparation of reactive sol-gel materials by the entrapment of stable nitroxyl radicals, comprising polymerizing at least one monomer of the formula $M(R)_n(P)_m$ belonging to the group of metal- or semimetal alkoxides, metal esters or semi-metal esters, where M is a semi- or a metallic element, R is an hydrolizable substituent, a is an integer of 1 to 6, P is a non-polymerizable substituent and m is an integer of 0 to 6, under acidic, neutral or basic conditions in the presence of stable di-tertiary-alkyl nitroxyl radicals or its precursors of formula



wherein A represents a chain of preferably two or three atoms, in particular carbon atoms (methylene groups) or a combination of one or two carbon atoms with oxygen or nitrogen atom, to form a gel at room temperature, containing the said dopant trapped therein,

- 24 -

5 followed by a drying step chosen among low pressure (under 70mm Hg; and preferably 15mm Hg) liophilisation to yield an areogel powder, a mild heat treatment (lower than 100° C, and preferably at 45° C) at atmospheric pressure to form a porous xerogel, coating of the gel on a mesoporous inorganic oxide (e.g. pumice stones) followed by solvent removing at low pressure (preferably at 15 mm Hg).

10 42. A process where an organic primary or secondary alcohol is dissolved in an organic solvent or in water and is oxidised in the presence of a doped material prepared as defined by claim 41, and in the presence of a primary oxidant chosen among Cu (II) salts, an hypobromite, an hypochlorite, a Cu (I) salt along with
15 oxygen bubbled through the solution.

43. A continuous process as defined in claim 2 where the oxidised product is removed while the alcoholic substrate is processed and the catalytic material is retained in the solution.

20 44. A process for the preparation of catalytic materials, a process of alcohol oxidation and a catalytic material as aforescribed.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/IT 99/00063

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 B01J31/02 B01J37/03 C07C51/235

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 B01J C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	A. SHAMES ET AL.: "In situ EPR study of sol-gel processes" JOURNAL OF NON-CRYSTALLINE SOLIDS, vol. 175, 1994, pages 14-20, XP002108351 cited in the application see page 15, column 2 ---	1-23, 41, 44
X	KAZUNORI MATSUI ET AL.: "ESR Study of a Nitroxide Radical in Sol-Gel Glasses" JOURNAL OF SOL-GEL SCIENCE AND TECHNOLOGY, vol. 9, 1997, pages 273-277, XP002108352 cited in the application see page 274, column 1 ---	1-23, 41, 44
-/--		



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

6 July 1999

Date of mailing of the international search report

21/07/1999

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Schwaller, J-M

INTERNATIONAL SEARCH REPORT

International Application No

PCT/IT 99/00063

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	HEERES A. ET AL.: "Synthesis of alpha and beta-D-glucopyranonate 1-phosphate and alpha-D-glucopyranuronate 1-fluoride: intermediates in the synthesis of D-glucuronic acid from starch" CARBOHYDRATE RESEARCH, vol. 299, 1997, pages 221-227, XP002108353 cited in the application	
A	US 5 292 801 A (D. AVNIR ET AL.) 8 March 1994 cited in the application	

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/IT 99/00063

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5292801 A	08-03-1994	IL 93134 A	20-11-1997
		AT 166459 T	15-06-1998
		DE 69129422 D	25-06-1998
		DE 69129422 T	07-01-1999
		EP 0439318 A	31-07-1991
		JP 6122521 A	06-05-1994
		US 5650311 A	22-07-1997
		US 5300564 A	05-04-1994
		US 5824526 A	20-10-1998
		US 5371018 A	06-12-1994
		US 5308495 A	03-05-1994